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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
WAX, ROBERT A	
ART UNIT	**PAPER NUMBER**
1653	

DATE MAILED: 10/28/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/726,734	KNUDSEN, LOTTE BJERRE	
	Examiner	Art Unit	
	Robert A. Wax	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-71* is/are pending in the application.

4a) Of the above claim(s) *30-71* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *02262004, 06012004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Restriction to one of the following inventions is required under 35 U.S.C. 121:

   I. Claims 1-29, drawn to method for treating diabetes or diabetes related diseases, classified in class 514, subclass 12.

   II. Claims 30-45, drawn to pharmaceutical composition, classified in class 514, subclass 12.

   III. Claims 46-71, drawn to a method for increasing the number or size of beta-cells in a subject or stimulating beta-cell proliferation in a subject, classified in class 514, subclass 12.

The inventions are distinct, each from the other because of the following reasons:

2. Inventions I and II are related as process of use and product. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case the process for using the product as claimed can be practiced with another materially different product such as GLP-1.

3. Inventions I and III are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of

operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the method of treating diabetes of Group I and the method for increasing the number or size of beta-cells in a subject or stimulating beta-cell proliferation in a subject of Group II do not require each other for their practice; have separate utilities, and are physically, chemically and biologically different from each other. These groups have acquired separate status in the art and separate fields of search as further evidenced by their separate classification.

4. Inventions II and III are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case the process for using the product as claimed can be practiced with another materially different product such as GLP-1.

5. During a telephone conversation with Richard Bork on September 26, 2005 a provisional election was made with traverse to prosecute the invention of Group I, claims 1-29. Affirmation of this election must be made by applicant in replying to this Office action. Claims 30-71 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Priority

6. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Information Disclosure Statement

7. The information disclosure statements filed February 26, 2004 and June 1, 2004 have been considered. Please see the attached initialed PTO-1449s.

Claim Rejections - 35 USC § 112, First Paragraph, Enablement

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claim 23 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 23 reads on administration of exendin and thiazolidinedione at suboptimal levels. The scope of the instant claims is not commensurate with the enablement of the instant disclosure, because practice of the claimed invention would require undue

experimentation by an artisan of ordinary skill in the art. That is, one of skill in the art would not know how to treat diabetes or a related disease with amounts of medication that are not the best doses to use.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

In the instant case, (1) the amount of experimentation is large since many trials would need to be run to determine what suboptimal level would be best to use; (2) the amount of guidance provided by the specification is nil since there is no discussion of how to determine what suboptimal dosage might have an effect. Continuing, (3) the

specification is totally devoid of any working examples; as for the next Wands factor, (4) the nature of the invention is combined use of exendin-4 and thiazolidinedione for treatment of diabetes or a diabetes-related disease. The prior art (5) shows that it is well known to use either ingredient alone and, as explained below, both Du Bois and Matsuno et al. render it obvious to use them together; (6) the relative level of skill in this art is very high; (7) the predictability of the art is zero since there is no telling from usual dosages which suboptimal dosages might work. Finally, (8) the claims are relatively broad since the range of dosages is so wide.

Based on this analysis, the conclusion that it would require undue experimentation to practice the instant invention is inescapable.

10. Claim 28 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 28 reads on administration of exendin-4 and thiazolidinedione in amounts and for a sufficient time to produce a synergistic effect. The scope of the instant claims is not commensurate with the enablement of the instant disclosure, because practice of the claimed invention would require undue experimentation by an artisan of ordinary skill in the art. That is, one of skill in the art would not know how to treat diabetes or a related disease with amounts of medication that are not the best doses to use.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

In the instant case, (1) the amount of experimentation is huge because three separate dose response curves need to be generated, one for each ingredient alone at all dosages and one for the combination in all proportions. Each dose response curve requires many measurements; (2) the amount of guidance provided by the specification is zero since, although information is given about tests done at particular concentrations, the data are missing from the specification. The test alluded to in the specification would be insufficient to establish synergistic results anyway since the

entire range of dosages and proportions is not covered. Continuing, (3) the specification is totally devoid of any working examples; as for the next Wands factor, (4) the nature of the invention is treatment of diabetes orf a diabetes-related disease with a synergistic combination of exendin-4 and a thiazolidinedione. The prior art (5) shows that it is well known to use either ingredient alone and, as explained below, both Du Bois and Matsuno et al. render it obvious to use them together; (6) the relative level of skill in this art is very high; (7) the predictability of the art is zero since there is no way of knowing which proportions might work in a synergistic fashion. Finally, (8) the claims are enormously broad because they read on any combination of ingredients that provide synergistic results.

Further, Tallarida (Drug Synergism and Dose-effect Analysis, Chapman & Hall/CRC, Boca Raton, 2000, pp. 1-13) and Berenbaum ("Synergy, additivism and antagonism in immunosuppression," Clin Exp Immunol 28:1-18, 1977) disclose that to demonstrate the synergistic effect of two treatment agents, one must first prepare a dose-response curve for each agent alone (see Fig. 1 of Berenbaum). One must also prepare a number of combination treatments containing varying amounts of each agent. The results of all the treatments, each agent alone and the various combinations must be compared and analyzed quantitatively and statistically. The discussion on p. 2 of Berenbaum describes how the value obtained by measuring a response achieved by administering two pharmaceutical treatment agents is often mistaken for synergy when in reality it is the same as the effect obtained by using either agent alone. That is, the effect produced by administering agent A in a particular amount (e.g., x mg) and agent B in a

particular amount (e.g., y mg) is the same as the one obtained by administering that total amount of agent A (x + y mg). Berenbaum also provides an algebraic method and a geometric method for determining the nature of the interaction of two agents (see pp. 3-5). To produce a graph such as Fig. 2 (p. 5), a particular response (effect) must be achieved by administering each agent alone. Different doses of agent A and different doses of agent B create the axes. A line is drawn between the two intercepts (the additivism line). A number of combinations of agent A and agent B, containing varying amounts of A and varying amounts of B, are tested, and the response is measured. The combinations producing the response achieved in the amount equal to that of the intercept points are determined and plotted as data points on the graph. If these data points fall below the additivism line, the effect of the combination is considered to be synergistic. If the data points fall above the additivism line, the effect is considered to be antagonistic. Tallarida discloses a similar analysis (see pp. 5-9). Tallarida also discloses that synergism analysis applies not only to pharmaceutical agents, but also to situations such as fertilizer or pesticides applied to crops to improve crop yield and to any pair of compounds that act similarly (see p. 1-2). Applicant has not provided this type of data in the specification, that is, dose-response data for the exendin-4 and thiazolidinedione alone and in combinations of varying amounts of each.

Based on this analysis, the conclusion that it would require undue experimentation to practice the instant invention is inescapable.

Claim Rejections - 35 USC § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

12. Claims 1-5, 16-19 and 29 are rejected under 35 U.S.C. 102(e) as being anticipated by Matsuno et al.

Matsuno et al. teach treatment of humans for diabetes or many diabetes-related diseases (listed in claim 25, for example) comprising administration of their inventive compound in combination with one to three other medicaments selected from a list including exendin-4 and some examples of thiazolidinediones (see claim 24). Since additional ingredients are not excluded from the claimed combination of exendin-4 and thiazolidinediones, this teaching anticipates the above claims.

Claim Rejections - 35 USC § 103

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

14. Claims 1-22, 24-27 and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Matsuno et al. in view of the prior art cited in the specification.

The teachings of the reference are outlined above.

The specification is replete with disclosures of known exendin-4 compounds and known thiazolidinediones.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to follow the teachings of Matsuno et al. and treat diabetes or other diabetes-related diseases with their inventive compound and add both exendin-4 and any of the thiazolidinediones to the combination with the expectation of beneficial results. Determination of the exact dosages to use is within the ordinary level of skill in the art and, thus, the limitations of claims 24-27 would have been obvious to one of ordinary skill in the art. In view of the disclosures of known exendin-4 compounds and known thiazolidinediones in the specification; selection of any of these is considered to be within the ordinary level of skill in the art as well. Said person of ordinary skill would expect any of the interchangeable compounds to work similarly well, thus, the limitations of claims 5-22 would have been obvious to one of ordinary skill in the art.

15. Claims 1-22, 24-27 and 29 are rejected under 35 U.S.C. 103(a) as obvious over Du Bois in view of the prior art cited in the specification.

Du Bois teaches treatment of diabetes or many diabetes-related diseases (listed in claim 11, for example) comprising administration of their inventive compound in combination with at least one other medicament (see column 24, lines 66-67) selected from a list including exendin-4 (see column 24, line 28) and many examples of thiazolidinediones (see column 24, lines 28-30).

The specification is replete with disclosures of known exendin-4 compounds and known thiazolidinediones.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to follow the teachings of Du Bois and treat diabetes or other diabetes-related diseases with her inventive compound and add both exendin-4 and any of the thiazolidinediones to the combination with the expectation of beneficial results. Determination of the exact dosages to use is within the ordinary level of skill in the art and, thus, the limitations of claims 24-27 would have been obvious to one of ordinary skill in the art. In view of the disclosures of known exendin-4 compounds and known thiazolidinediones in the specification; selection of any of these is considered to be within the ordinary level of skill in the art as well. Said person of ordinary skill would expect any of the interchangeable compounds to work similarly well, thus, the limitations of claims 5-22 would have been obvious to one of ordinary skill in the art. While treatment of humans does not appear to be stated explicitly in the text, the discussion of the diseases to be treated makes it clear that human treatment is contemplated, thus, the limitation of claim 29 would have been obvious to one of ordinary skill in the art.

Conclusion

16. No claim is allowed.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert A. Wax whose telephone number is (571) 272-0623. The examiner can normally be reached on Monday through Friday, between 9:00 AM and 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon P. Weber can be reached on (571) 272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Robert A. Wax
Primary Examiner
Art Unit 1653

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